The AIDS epidemic was heralded in initial CDC reports in 1980 of a cluster of cases of Pneumocystis carinii pneumonia (PCP) among homosexual and bisexual men in New York and California. Since the beginning of the epidemic, pulmonary diseases have been the major causes of illness and disease. Twenty years into the epidemic this is still the case. Pulmonary infection is a well established feature of HIV infection, and opportunistic pulmonary disease, most notably tuberculosis and PCP are most frequently AIDS defining diagnoses. Autopsy studies show that the lung is the most common site for AIDS-associated disease processes being affected in 90% of patients. The lung, along with the spleen and lymph nodes is also an important site for HIV replication. There is now clear evidence that HIV-1 and 2 enter the lung early in the natural history of HIV infection. Much of our knowledge on the varied lung manifestations of HIV have come from the “Pulmonary Complications of HIV infection Study”. This major prospective study carried out from November 1988 through February 1990, prospectively studied 1353 HIV +ve adults to determine the prevalence, incidence and types of lung disease encountered in this cohort. The subjects were followed up for a mean period of 53 months and the spectrum of HIV related disorders seen is as follows:

1. **Bacteria**
   a. Higher incidence of URTI’s, acute bronchitis and acute sinusitis.
   b. Bacterial pneumonia (Strep pneumoniae, H in uenzae, Staph aureus, M catarrhalis, pseudomonas aeruginosa)
   c. Mycobacteria tuberculosis
   d. Nocardia asteroides
   e. Rhodococcus equii
   f. Mycobacterium avium intracellulare (MAC)

2. **Protozoa**
   a. P. Carinii (PCP)
   b. Strongyloides stercoralis
   c. Toxoplasma gondii

3. **Viruses**
   a. Cytomegalovirus
b. Adenovirus

c. Herpes simplex virus

4. Fungi
   a. Aspergillus fumigatus
   b. Cryptococcus neoformans
   c. Blastomyces dermatitides
   d. Coccidioides immitis
   e. Histoplasma capsulatum

5. Malignancies
   a. Kaposi sarcoma
   b. Non Hodgkin lymphoma
   c. Carcinoma of the lung

6. Other pulmonary disorders seen with higher frequency:
   a. Lymphocytic interstitial pneumonia
   b. Nonspecific interstitial pneumonia
   c. Bronchiolitis obliterans organizing pneumonia (BOOP)
   d. Sarcoidosis
   e. Primary pulmonary hypertension

This talk will focus on only three of these varied manifestations: Tuberculosis, PCP, and Kaposi’s sarcoma.

Tuberculosis
The initial link between TB and HIV was not apparent till about 5 years into the HIV epidemic it became apparent that the annual steady decline in TB prevalence in the U.S (around 5%/ year) had not only reduced (to 0.2%) but then actually increased for the first time in 35 years (by 2.6% in 1986). This was followed by studies from across sub-Saharan Africa which showed dramatic increases in reported TB cases; up 86% in Tanzania, 140% in Burundi and a staggering 180% in Malawi. It soon became apparent that this rise in TB prevalence rates from developed and developing parts of the world was secondary to HIV. In 1993 the CDC listed pulmonary TB as an AIDS defining diagnosis. The reasons for this synergy are obvious; CD4 + T lymphocytes play a central role in defense against tuberculosis. HIV causes a selective depletion of CD4 cells decreasing the capacity of these cells to produce interferon gamma. Thus HIV markedly increases TB risk. From the stand point of a clinician;

1. Reactivation of latent tuberculosis is common.
2. These patients are more prone to becoming initially infected with tuberculosis
3. They rapidly develop disease from newly acquired infection.
4. Documented cases of re infection after initial successful treatment are not uncommon and may account for some relapses.
5. The clinical picture has changed.
6. There is a marked increase in mortality despite treatment.

Clinical Features of TB in HIV +ve Patients
TB is often the earliest OI in the natural history of the HIV +ve patient occurring at higher median CD4 counts than most other OI’s. Symptoms and signs cannot distinguish TB from other OI’s except for the presence of PUO and weight loss > 10 kgs both of which occur more frequently with TB than other OI’s. Literature is replete with so called “atypical features” of TB in the HIV +ve patient. We now know that the spectrum of clinical and radiological features is no different from those in the sero-negative TB patient. Instead, the manifestations depend upon the CD4 count; “typical” when CD4 counts are preserved, and “atypical” when CD4 counts are low. These atypical findings include focal, nodular, often lower lobe infiltrates. There is also a high incidence of extra-pulmonary TB.
Diagnosis
of tuberculosis in the HIV +ve patient is more difficult because apart from atypical radiology, the tuberculin test is often false negative and sputum analysis is more often negative. A high index of suspicion is needed and invasive tests like bronchoscopy may improve the yield. Because of the pauci-bacillary, extra-pulmonary nature of TB in these patients it is important to sample multiple extra-pulmonary sites like blood, urine, stools and lymph nodes from which yields of AFB culture may vary from 36-87%.

Treatment
Whilst the treatment of TB in the HIV+ve patient is essentially the same as in the sero-negative patient and the improvement in symptoms, radiology and sputum conversion occurs with the same frequency, the news is not all good. These patients have an increased incidence of adverse effects with anti-TB drugs and increased frequency of paradoxical reactions. Despite treatment they have a higher mortality, often from other opportunistic infections. Besides, there is an increased recurrence rate of tuberculosis even after initial successful treatment. A recent study from Jill Murray’s group of South African miners found the TB-HIV+ve group had a 26 x higher mortality than the TB-HIV-ve group with much of the excess mortality being from non-tuberculosis AIDS related conditions. (Murray J. AJRCCM 1999).

Despite these differences, the drugs, principles of use and even duration of treatment remain unchanged in the HIV+ve TB patient. Important interactions however occur in the patient concurrently receiving anti-TB drugs and anti-viral therapy which pose a quandary for health providers. These mainly focus on the drug-drug interactions between rifamycins and most protease-inhibitors and some NNRTIs because of rifamycin being a potent inhibitor of the cytochrome P450-3A system. The consequence of such an interaction is greatly reduced levels of the PI or NNRTI and increased levels of rifamycin. The talk will discuss this complex topic in greater detail.

Paradoxical Reactions
are another issue of great relevance to the clinician. They are defined as transient worsening or appearance of new symptoms, signs or radiographic manifestations of TB occurring after initiation of treatment and are not the result of treatment failure or a second process. The mechanism of these reactions is believed to be restoration of immunity towards mycobacterial antigens. The clinical consequences vary from subtle rise in temperature and worsening lung infiltrates to dramatic and life threatening acute respiratory failure or expanding brain masses. The treatment involves steroids and discontinuation of the drugs in the case of serious reactions.

Impact of HAART
With the widespread use of HAART in the Western world, there are gratifying reports of 5 fold reduction in the incidence of TB in HIV+ve patients receiving HAART. Sadly it is a reflection of the injustice of our times that less than 1% of patients in the developing world who bear the brunt of HIV and TB have access to these drugs.

Pneumocystis Carini Pneumonia (PCP):
Prior to the onset of the AIDS epidemic PCP was an extremely rare cause of pneumonia in the immunocompromised patient, being responsible for no more than 100 cases a year. With the onset of the AIDS epidemic it soon became recognized that this was the commonest OI and the most frequent AIDS defining disease in the developed world.

Taxonomy
After decades of debate, sophisticated molecular phylogeny studies have now established that PCP
is a fungus and not a protozoan. Three major forms of the organism have been recognized; 1. the trophozoite, 2. the cyst, and 3. the precyst.

Incidence of PCP in the Pre-HAART era
At the onset of the AIDS epidemic, PCP represented the commonest AIDS index diagnosis, as well as the most common AIDS index diagnosis. Between 1982-1987, the incidence of PCP ranged from 44% to 74% in series from the West. Lower rates were reported from Africa and Asian countries where it was felt that PCP was a rare pathogen. A number of factors could have been responsible for this including absence of the organism from the environment, less exposure to the organism, difference in host susceptibility, earlier deaths in AIDS patients from more pathogenic organisms like M tuberculosis or the lack of diagnostic facilities. To my mind the latter is the most likely factor; in our tertiary referral centre in Mumbai with ready access to fibreoptic bronchoscopy and the advent of immuno uorescent staining techniques, PCP is one of the commonest OI’s encountered.

Clinical Features
It is now recognized that in contrast to HIV seronegative immunocompromised patients where the onset is acute, in the HIV+ve population the onset of PCP is insidious with symptoms being present for weeks and sometimes months before the diagnosis is made. The presenting symptoms are non-specific and include fever, dyspnea on exertion and rest and a non-productive cough. The most frequent physical finding is tachypnea. Routine lab results typically reveal normal WBC counts, anemia and hypoalbuminemia and raised LDH levels that correlate with disease severity. Hypoxemia and desaturation after minimal exercise are also characteristic.

Radiology
Typical manifestations are diffuse, bilateral, interstitial or alveolar infiltrates.
Atypical manifestations described range from normal Xrays to upper lobe infiltrates, cysts, pneumothorax, pleural effusion, nodular lesions, cavitation and hilar adenopathy. Some of these atypical manifestations are more common in patients taking aerosolized pentamidine prophylaxis.
CT features have been well described and include a ground glass patchy alveolar and interstitial pattern.

Therapy of PCP
The treatment of choice for mild, moderate and severe pneumonias remains TMP-SMX because of its efficacy, low cost and ease of administration via oral or IV routes. The standard adult dose consists of 15-20 mg/kg/day of the TMP component and 75-100 mg/kg/day of the SMX component given orally or IV in 3 to 4 divided doses for 21 days. Severe toxicity requiring discontinuation of therapy has been reported in 0 – 57% of patients.
Other treatments for PCP in patients unable to tolerate TMP-SMX include intravenous pentamidine, atovaquone, clindamycin-primaquine, trimethoprim-dapsone and trimetrexate.
Corticosteroids have an extremely useful role as adjunctive therapy in patients with PCP and impending respiratory failure. They reduce the possibility of declining oxygenation and need for ventilatory support by approximately one-half in patients with moderate PCP defined as PaO2 < 70 mmHg. For full efficacy it is recommended that they be used within 72 hours of starting anti-PCP therapy. Small doses have been recommended; no more than 40 mg of prednisolone twice daily for 5 days, followed by 40 mg daily for 5 days and then 20mg daily for 11 days till completion of therapy.

Prophylaxis
A single double strength tablet of TMP-SMX remains the prophylactic treatment of choice and should
be offered to all patients with CD4 counts < 200 / mm3. Other drugs used for prophylaxis include; TMP-SMX single strength tablet daily, TMP-SMX DS 3 x a week, dapsone 100mg daily, dapsone-pyrimethamine once weekly or nebulised pentamidine 300mg monthly via a Respigard 2 nebuliser.

Declining PCP Prevalence
With the advent of prophylaxis and HAART the incidence of PCP has greatly declined over the last 5 years of the epidemic in the developed world. In the Prospective Study of Complications of HIV infection a cohort of 1116 HIV+ve patients followed up to 1992, only 3.9% of patients developed PCP.

Kaposi Sarcoma (KS)
Kaposi Sarcoma is a previously rare tumor occurring 20,000 times more frequently in those with AIDS than in the general population. Sequences of human herpes virus 8 have recently been isolated in all patients with KS and this virus plays a role in the pathogenesis of KS. Whilst AIDS associated KS presents with cutaneous disease the lungs are not infrequently affected. Pulmonary KS occurs in a third of KS patients and at autopsy almost 50% of all KS patients will be found to have lung involvement. Pulmonary manifestations are dyspnea and cough and the radiological patterns include nodules, masses, and mediastinal adenopathy. Endobronchial lesions result in distinctive bright red lesions seen at branching of the bronchial tree and occasionally in the trachea.

Treatment
This is an aggressive malignancy and the prognosis is poor. Chemotherapy and radiotherapy have been tried with little success and palliative treatment is the preferred approach.

Suggested Reading
3. Udwadia ZF. Pneumocystis Pneumonia: Taming the beast. The Indian Practitioner 1999;52;9;593-594.